

Experiment Number: S0553

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: Gavage, IV

Compound: 3'-Azido-3'-deoxythymidine/ Analyte: 3'-Amino-3'-deoxythymidine

Request Time: 10:03:16

Species/Strain: Mouse/B6C3F1

CAS Number: 30516-87-1

Lab: RTI

Male

Treatment Group (mg/kg)

100 AZT/0 RIF IV Plasma<sup>a,c</sup>

100 AZT/0 RIF Gavage Plasma<sup>a,b</sup>

Cmax_obs (ug/mL)	0.592	0.459
Tmax_obs (minute)	15	20
Beta Half-life (minute)	34.6	
AUC_0-T (ug*min/mL)	37.9	32.0

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Female

Treatment Group (mg/kg)

100 AZT/0 RIF IV Plasma<sup>a,e</sup>

100 AZT/0 RIF Gavage Plasma<sup>a,d</sup>

Cmax_obs (ug/mL)	0.401	0.453
Tmax_obs (minute)	10	40
Beta Half-life (minute)	39.5	
AUC_0-T (ug*min/mL)	25.8	60.4

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Treatment Group (mg/kg)

100 AZT/0 RIF IV Plasma<sup>a,k</sup>

100 AZT/0 RIF Gavage Plasma<sup>a,j</sup>

Cmax_pred (ug/mL)	175	64.9
Tmax_pred (minute)		10
Beta Half-life (minute)	19.9	24.9
Cl (mL/min/kg)	28.1	
Cl <sub>1_F</sub> (mL/min/kg)		38.6
MRT (ug*min/mL)	21.5	34.1
AUC <sub>inf_pred</sub> (ug*min/mL)	3555	2588
F		0.73

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CAS Number: 30516-87-1

Lab: RTI

Female

Treatment Group (mg/kg)

100 AZT/0 RIF IV Plasma<sup>a,k</sup>

100 AZT/0 RIF Gavage Plasma<sup>a,j</sup>

Cmax_pred (ug/mL)	179	70.1
Tmax_pred (minute)		5
Beta Half-life (minute)	22.4	25.2
Cl (mL/min/kg)	23.5	
Cl <sub>1_F</sub> (mL/min/kg)		35.4
MRT (ug*min/mL)	26.2	37.1
AUC <sub>inf_pred</sub> (ug*min/mL)	4247	2825
F		0.67

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Route: Gavage, IV

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**Toxicokinetics Data Summary**

**Compound:** 3'-Azido-3'-deoxythymidine

**Analyte:** 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine

**CAS Number:** 30516-87-1

**Request Date:** 7/11/2023

**Request Time:** 10:03:16

**Lab:** RTI

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Male

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**Treatment Group (mg/kg)**

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**100 AZT/0 RIF IV Plasma<sup>a,g</sup>**

**100 AZT/0 RIF Gavage Plasma<sup>a,f</sup>**

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Cmax_obs (ug/mL)	0.916	0.817
Tmax_Obs (minute)	15	20
Beta Half-life (minute)	13.7	
AUC_0-T (ug*min/mL)	28.5	47.9

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Route: Gavage, IV

Species/Strain: Mouse/B6C3F1

**Toxicokinetics Data Summary**

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**Analyte:** 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine

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Female

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**Treatment Group (mg/kg)**

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**100 AZT/0 RIF IV Plasma<sup>a,h</sup>**

**100 AZT/0 RIF Gavage Plasma<sup>a,i</sup>**

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Cmax_obs (ug/mL)	0.709	0.575
Tmax_Obs (minute)	20	15
Beta Half-life (minute)	17.1	
AUC_0-T (ug*min/mL)	15.9	12.0

**Experiment Number:** S0553

**Route:** Gavage, IV

**Analyte:** 3'-Amino-3'-deoxythymidine/3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine/3'-Azido-3'-deoxythymidine

**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**

**Compound:** 3'-Azido-3'-deoxythymidine

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## LEGEND

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### MODELING SOFTWARE

PCNONLIN software Version 4 .2,

### MODELING METHOD & BEST FIT MODEL

<sup>a</sup>PCNONLIN software Version 4 .2, SCI Software, Apex, NC, non-compartmental analysis

### EXCEPTIONS

<sup>b</sup>AMT t<sub>1/2</sub>Beta were calculated from 15 to 150 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 180 minutes.

<sup>c</sup>AMT t<sub>1/2</sub>Beta were calculated from 15 to 150 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 240 minutes.

<sup>d</sup>AMT t<sub>1/2</sub>Beta were calculated from 15 to 150 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 300 minutes.

<sup>e</sup>AMT t<sub>1/2</sub>Beta were calculated from 15 to 150 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 240 minutes.

<sup>f</sup>GAZT t<sub>1/2</sub>Beta were calculated from 15 to 60 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 180 minutes.

<sup>g</sup>GAZT t<sub>1/2</sub>Beta were calculated from 15 to 60 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 60 minutes.

<sup>h</sup>GAZT t<sub>1/2</sub>Beta were calculated from 15 to 60 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 40 minutes.

<sup>i</sup>GAZT t<sub>1/2</sub>Beta were calculated from 15 to 60 minutes. For AUClast (AUC<sub>0-T</sub>) the time the last plasma sample was obtained was 40 minutes.

<sup>j</sup>20-180 minutes is the time interval over which t<sub>1/2</sub>Beta was calculated. Cl is apparent clearance.

<sup>k</sup>2.5-240 minutes is the time interval over which t<sub>1/2</sub>Beta was calculated. C<sub>max</sub> equals C<sub>0</sub> calculated by back extrapolation of the plasma concentration vs. time curves.

### ANALYTE

3'-Amino-3'-deoxythymidine

3'-Azido-3'-deoxythymidine

3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine

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TK PARAMETERS

C<sub>max</sub> = Observed or Predicted Maximum plasma (or tissue) concentration

T<sub>max</sub> = Time at which C<sub>max</sub> predicted or observed occurs

Beta Half-life = Half-life for the alpha phase

Cl = Clearance, includes total clearance

Cl<sub>1\_F</sub> = Apparent clearance of the central compartment, also Cl<sub>1\_F</sub> for gavage groups in non-compartmental model

MRT = Mean residence time

AUC<sub>0-T</sub> = Area under the plasma concentration versus time curve, AUC, from time t<sub>i</sub> (initial) to t<sub>f</sub> (final), AUC<sub>last</sub>

AUC<sub>inf\_pred</sub> = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Blood was analyzed for 3'-Azido-3'-deoxythymidine (AZT), metabolite 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine (GAZT), and metabolite 3'-Amino-3'-deoxythymidine (AMT) by HPLC with UV detection. Limit of detection (LOD) was estimated to be 0.042 ug/mL for AZT, 0.078 ug/mL for GAZT, and 0.015 ug/mL for AMT.

TK\_GAVAGE PLASMA

100 mg/kg AZT/0 mg/kg RIF Male and Female

Animals weighed between approximately 20 and 30 g and were approximately 70-80 days of age at dosing. Animals received a single bolus dose either as an intravenous injection or oral gavage. Blood was collected at 13-14 timepoints from at least 3 mice per timepoint.

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TK PARAMETERS PROTOCOL (cont'd)

#### ANALYSIS METHOD

Blood was analyzed for 3'-Azido-3'-deoxythymidine (AZT), metabolite 3'-Azido-3'-deoxy-5'-beta-D-glucopyranurosylthymidine (GAZT), and metabolite 3'-Amino-3'-deoxythymidine (AMT) by HPLC with UV detection. Limit of detection (LOD) was estimated to be 0.042 ug/mL for AZT, 0.078 ug/mL for GAZT, and 0.015 ug/mL for AMT. Nondetectable data points and points below the estimated detection limits were treated as missing data points. The one-compartment model fit AZT data best with simultaneous solution of combined data sets of the different groups until approximately 180 minutes post-dosing.

#### TK\_INTRAVENOUS PLASMA

##### 100 mg/kg AZT/0 mg/kg RIF Male and Female

Animals weighed between approximately 20 and 30 g and were approximately 70-80 days of age at dosing. Animals received a single bolus dose either as an intravenous injection or oral gavage. Blood was collected at 13-14 timepoints from at least 3 mice per timepoint.